

REMARKS

No claim amendments have been effected by this Supplemental Response. Claims 454-575 which were submitted in Applicants' November 20, 1998 Amendment Under 37 C.F.R. § 1.116 continue to be under present examination in this application.

Applicants and their undersigned attorney wish to take this opportunity to inform the U.S. Patent and Trademark Office and the Examiner of recent favorable developments in the European Patent Office affecting their corresponding European Patent Application No. 88104962.1, that was published on October 5, 1988 as European Patent Publication No. O 285 058 A2. This European application is a divisional of another European application, both of which are based upon the priority document, U.S. Patent Application Serial No. 06/391,440, filed on June 23, 1982. Serial No. 06/391,440 was the first-filed patent application in the family to which the present U.S. application is a member. A copy of each of EP O 285 058 A2 and the separately issued search report are attached as Exhibits A and B, respectively.

Applicants' attorneys received a letter dated December 7, 1998 from their European associates, reporting on an Official Communication issued by the EPO on October 6, 1998. In their December 7th letter, the European associates wrote:

The Examiner holds the view that the revised claims submitted with our last reply meet the requirements of Art. 123(2) EPC and confirms their patentability with regard to novelty and inventive step [obviousness]. However, he has several objections with respect to clarity and also objects to claim 32 alleging that it is directed to a method of treatment. Furthermore, he requests the re-arrangement of the claims in groups relating to variants of a certain feature.

[bold, italic & underline added]

In their December 7th letter, the European associates also wrote:

We enclose a draft of a new claims set which takes into account the Examiner's objections and suggestions and wherein we have also introduced multiple back references.

Dean L. Engelhardt, et al.  
Serial No.: 08/479,997  
Filed: June 7, 1995  
Page 3 (Supplemental Response to Applicants' November 20, 1998 Amendment  
Under 37 C.F.R. § 1.116 – January 19, 1999)

A copy of the European associates December 7, 1998 letter, the October 6, 1998 Official Communication from the EPO, and the draft set of claims 1-37 referenced in the former Communication, are attached as Exhibits C, D and E, respectively.

It is believed that this information is of relevance to the present application, the previous claims of which were finally rejected by the Examiner for obviousness over a combination of Gohlke et al., U.S. Patent No. 4,378,458, filed on March 30, 1981, in view of Sodja et al., "Gene mapping and gene enrichment by the avidin-biotin interaction: use of cytochrome-c as a polyamine bridge," Nucleic Acids Research 5(2):385-401 (1978). A copy of previously cited Sodja et al. is attached as Exhibit F. Sodja's cited paper was co-authored by Dr. Norman Davidson who led the group at California Institute of Technology that was investigating gene mapping and gene enrichment in the late 1970s.

As indicated in Applicants' previous responses, including their November 20, 1998 Amendment Under 37 C.F.R. §1.116 (see page 34, last paragraph, through page 35, first paragraph), Sodja et al. rely on a drastic periodate oxidation chemistry to break open the ribose sugar aldehyde ring of RNA. The periodate oxidation chemistry requires two 2', 3' OH groups on the ribose aldehyde in the *cis* configuration, thus limiting the chemistry to RNA and preventing the use of DNA.

It turns out that in the European search report (Exhibit B) issued for Applicants' European application (EP 0 285 058 A2), another earlier Davidson paper, Angerer et al., "An Electron Microscope Study of the Relative Positions of the 4S and Ribosomal RNA Genes In HeLa Cell Mitochondrial DNA," Cell 9:81-90 (1976) was also cited as a "document considered to be relevant."<sup>1</sup> See Exhibit B,

<sup>1</sup> It is believed that the Angerer et al. 1976 Cell paper was submitted to the Patent and Trademark Office in an Information Disclosure Statement Under 37 C.F.R. §§1.56 & 1.97-1.98 filed on August 22, 1994 in connection with the immediate predecessor application, U.S. Patent Application Serial No. 08/046,004, filed April 9, 1993, now abandoned. A Supplemental Information Disclosure Statement Under 37 C.F.R. §§1.56 & 1.97-1.98 was also filed in the present application on September 18, 1995 to comply with the Examiner's request for 23 documents which may or may not have been included with the previous August 22, 1994 IDS. Applicants expect to furnish the Examiner shortly with a copy of all the Form PTO-1449 Information Disclosure Citation forms filed

page 1 of sheet titled "EUROPEAN SEARCH REPORT" at the top. See the last entry at the bottom of that page under the column labeled "DOCUMENTS CONSIDERED TO BE RELEVANT." A copy of Angerer et al. is attached as Exhibit G. Angerer et al. also disclose on page 81, right column, second full paragraph, the same identical and drastic periodate oxidation chemistry disclosed earlier by the cited Sodja et al. There, in Angerer et al. (Exhibit G), Davidson's group discloses:

Since at least five additional genes coding for tRNA were found in the HeLa mitochondrial genome, we decided to reinvestigate the arrangement of 4S RNA genes by using a newly developed method of labeling hybridized RNA with ferritin for direct electron microscopic examination (T.R. Broker, L. Angerer, N.D. Hershey, P. Yan, M. Pellegrini, and N. Davidson, manuscript in preparation). In this procedure, a small molecule, biotin, is covalently coupled to the oxidized 3' terminus of RNA molecules. The RNA is then hybridized to a DNA strand. The position of the RNA:DNA hybrid on the DNA strand is mapped by incubating with a covalent conjugate of the electron-opaque label ferritin with the protein avidin. The labeling reaction is based on the rapid and strong noncovalent association of avidin with biotin (Green, 1963).

[bold, italic and underline added]

Thus, a significant patent examining authority, the European Patent Office, has reached the sound conclusion that Applicants' corresponding invention claimed in Europe is indeed patentable over Angerer et al., a scientific publication that relies on the same periodate chemistry as Sodja et al. cited in the instant application. Both of their chemistries cause the same drastic ribose ring cleavage of RNA.

It is respectfully requested that the Examiner consider these developments involving Applicants' European application as being of possible relevance to the prosecution of the present U.S. application. Although the issue of periodate chemistry does not appear to have been specifically addressed in any communication issued by the EPO, it is clear that the Examining Division considered Angerer et al. that was cited in the European search report, and the Examining Division apparently concluded that no issue of novelty or inventive step was presented by Angerer et al. against Applicants' European patent claims,

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in connection with the present application and its predecessor (Serial No. 08/046,004) in order to ensure that all art-related documents have been cited and considered in the current prosecution.

Dean L. Engelhardt, et al.  
Serial No.: 08/479,997  
Filed: June 7, 1995  
Page 5 (Supplemental Response to Applicants' November 20, 1998 Amendment  
Under 37 C.F.R. § 1.116 – January 19, 1999)

which are arguably broader than their present U.S. claims, 454-575. Instead, the Examining Division raised other prior art documents, but has since concluded, judging from the latest October 6, 1998 Official Communication (Exhibit D), that Applicants' European claims (Exhibit E) are novel and moreover, contain an inventive step, that is to say, are patentably unobvious.

Allowance of Applicants' European claims is expected the early part of this year. The allowance is expected in the typical form of a Rule 51(4) EPC Communication in which the EPO states its intent to issue a patent. As soon as it is received, Applicants' attorney will send a copy of the Rule 51(4) EPC Communication to the Examiner for his review and consideration.

Favorable consideration and action on claims 454-575 is respectfully requested.

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Dean L. Engelhardt, et al.  
Serial No.: 08/479,997  
Filed: June 7, 1995  
Page 6 (Supplemental Response to Applicants' November 20, 1998 Amendment  
Under 37 C.F.R. § 1.116 – January 19, 1999)

**SUMMARY AND CONCLUSIONS**

No amendments, additions or deletions to claims 454-575 have been made in this Supplemental Response.

No fee is believed to be due for this Supplemental Response. If any fee or fees are deemed to be due, however, authorization is hereby given to charge the amount of any such fee(s) to Deposit Account No. 05-1135, and to credit any overpayment thereto.

If it would be helpful to expediting prosecution of this application, Applicants' undersigned attorney may be contacted during normal daytime business hours at (212) 583-0100, or by facsimile, at (212) 583-0150.

Respectfully submitted,



Ronald C. Fedus  
Registration No. 32,567  
Attorney for Applicants

ENZO DIAGNOSTICS, INC.  
c/o ENZO BIOCHEM, INC.  
527 Madison Avenue, 9<sup>th</sup> Floor  
New York, New York 10022  
Telephone: (212) 583-0100  
Facsimile: (212) 583-0150